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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,117	02/22/2006	Richard L. Miller	58751US010	2906

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EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
05/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/595,117	MILLER ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11,14,17,20-22,27,34 and 36* is/are pending in the application.

4a) Of the above claim(s) *5-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,11,14,17,20-22,27,34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

The amendment filed on March 5, 2009 is acknowledged. Claims 1-8, 11, 14, 17, 20-22, 27, 34, 36 are pending.

Applicants' arguments, filed on March 5, 2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. Responses are limited to Applicants' arguments relevant to either reiterated or newly applied rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 7, 8, 11, 14, 17, 20-22, 27, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hedenstrom *et al.* (2002/0058674) and Mitra *et al.* (WO/2002/102377) in further view of Gordon *et al.* (20040014779).

'674 teaches method/system for treating condition associated with a mucosal surface, the system comprising an immune response modifier (IRM) compound chosen from imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, 1,2-bridged imidazoquinoline amines, and pharmaceutically acceptable salts thereof and an applicator device for applying the IRM compound to the mucosal surface. This system of IRM compounds and applicator may be used to treat conditions associated with mucosal surfaces such as cervical dysphasia and cervical intraepithelial neoplasia (abstract). '674 discloses the use of imiquimod in their example formulation Table 1 [0351] and Table 2 [0354]. However the language comprising in their claim 1 enables one skilled in the art to use any immune response modulators for the same purpose. '674 also teaches methods which are particularly advantageous for topical application to the cervix for treatment of cervical conditions such as cervical dysplasias including dysplasia associated with human papillomavirus (HPV) (instant claims 3-4) [0002]. '674 also teaches the compositions can be applied topically, particularly to non-cornified epithelial surfaces such as mucosal surfaces. Mucosal surfaces include mucosal membranes such as buccal, gingival, nasal, tracheal,

bronchial, gastrointestinal, rectal, urethral, ureteral, vaginal, cervical, uterine, etc. Depending on the IRM concentration, formulation composition, and mucosal surface, the therapeutic affect of the IRM may extend only to the superficial layers of the mucosal surface or to tissues deep to the surface [0333].

'674 further teaches that IRM can be formulated as a suppository and administered intravaginally using a suppository applicator [0343] or IRM can be topically applied to the cervical mucosa by using a direct cervical applicator, as previously described or using a cervical cap [0334] (instant claims 2, 7, 34, 36). This reads on instant claim 2 because it uses the same device to apply and when the device is removed after use it is removed from the same device. '674 teaches that single dose, randomized, double-blind, placebo controlled dose escalation study which evaluated five doses of imiquimod. 50, 100, 150, 200 and 250 mg of imiquimod in a cream formulation were applied to the cervix for eight hours [0348] (instant claim 8). '674 further teaches that although some of the beneficial effects of IRMs are known, the ability to provide therapeutic benefit via topical application of an IRM for treatment of a particular condition at a particular location may be hindered due to tissue irritation, formulation wash away, poor permeation or undesired systemic delivery of the topically applied compound. Accordingly, there is a need for new methods, formulations, and systems to provide the greatest therapeutic benefit from this class of compounds [0007]. This explains the limitation of claim 1 that the method of treatment should achieve immuno modulation with reduced irritation, and the disposable tampon's and cervical cup explained above.

'674 further teaches topical administration of a pharmacological agent to a tissue surface can provide localized therapeutic benefit without concomitant systemic effects. However,

topical application is often difficult or impossible due to the anatomical location of the tissue. In some cases, application of the agent to a general anatomical region that includes or surrounds the target tissue may be an alternative to direct topical application. But, if the agent has irritating properties, this alternative disadvantageously carries with it the possibility of irritating tissues surrounding the target tissue. In addition, even if the agent is non-irritating, regional application typically requires use of a greater volume or concentration of the agent to achieve a therapeutic result equivalent to that achieved by direct application to the target tissue [0008].

'674 further teaches that the uterine cervix is one example of a target tissue to which it is difficult to apply a topical agent. Relative to a standing position, the cervix is typically located at the uppermost portion of the vaginal cavity. However, while the cervix is located at the uppermost portion of the vaginal cavity, age, the stage of the estrous cycle, pregnancy, and other factors cause variability of the location of the cervix between different women and in the same woman at different stages of life [0009]. In addition, with the exception of certain body orientations, gravity tends to drain agents away from the cervix. Normal discharge and flow of fluids, both menstrual and non-menstrual, also drain away from the cervix. Thus, any applicator that is not capable of repeatedly delivering an appropriate amount of agent to the uppermost end of the vaginal cavity risks less than optimal treatment [0011]. Although '674 does not teach the removal of the device after two hours as in instant claim 11, one skilled in the art would know that the use of cervical cap or suppository depending on the state of life of the women's body it can be removed and inserted within this time period.

'674 does not teach the use of 1-(2-methylpropyl)-lH- imidazo [4,5-c] [1,5]naphthyridin-4-amine (CAS number 227318-71-0), the elected specie of the current invention.

'377 teaches the use of 1-(2-methylpropyl)-lH- imidazo [4,5-c] [1,5] naphthyridin-4-amine as an immune response modifier (IRM) as topical formulations and teach A" treatment site" means the site where the pharmaceutical composition is delivered to the patient. Treatment sites are typically local sites proximate to a lesion and generally include the gingival surfaces, periodontal pockets, or any other site that the drug could be delivered to the maxillary or mandibular tissue. The composition is typically delivered topically or by placing the composition in the subgingival space (periodontal pocket) (pg 37, ln 9-14). The transmucosal patches can remain adhered to the gingiva for about 1-24 hours. In a typical situation the patch will remain adhered for about 1-3 hours (pg 38, ln 13-16). The patches can be applied two times a week for three weeks. The patient can be reexamined at 1 month after completion of treatment and at three month intervals thereafter (pg 38, ln 6-12). This corroborates the IRM used in the cited reference can be used for mucosal application (instant claims 1, 17, 20, 21, 22, 27) and the treatment regimen is dictated by patients need and the physician's decision. The cited reference does not use imiquimod as an IRM.

'674 and '377 do not teach the IRM compounds being used as TRL7 agonist.

'779 teaches that many IRM compounds the activation of a TLR pathway of an organism may result in increased or decreased production of at least one cytokine. Because the ability to control cytokine levels can be useful in the treatment of cytokine-related conditions, the present

invention also provides methods of treating these conditions. It is possible that in certain embodiments, production of one or more cytokines will be induced, while the production of one or more other cytokines will be inhibited [0082].

'779 teaches that the present invention provides a method of treating an organism having a condition treatable by modulating a TLR-mediated cellular response. The method includes administering to the organism an IRM compound that activates a TLR-mediated cellular signaling pathway. The IRM compound may be an agonist of any suitable TLR (e.g., TLR6 or TRL7) [0083] (instant claim 14). Agents that activate the TLR pathway are expected to be particularly useful in the treatment of viral diseases and tumors such as intraepithelial neoplasias such as cervical intraepithelial neoplasia, human papillomavirus (HPV), and associated neoplasias [0085]. '779 specifically teaches the use of imiquimod [0023] and the instant claimed compound in para 0078 and IRM 7 in Table 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the '674, '779 and '377 because '779 teaches that instant claimed compound 1-(2-methylpropyl)-lH- imidazo [4,5-c] [1,5] naphthyridin-4-amine is a IRM that is useful in modulating TRL7 pathway to treat HPV or cervical intraepithelial neoplasia (cervical dysplasia symptom) just as imiquimod. '377 teaches that instant claimed compound can be used in a transmucosal application and '674 teaches that cervical mucosa and bucal mucosa are all transmucosal applications. '674 teaches the use of imiquimod in a cervical cap or suppository as a IRM useful for treating cervical dysplasia. One skilled in the art could very easily combine the teachings of '674, '779 and '377 to substitute 1-(2-methylpropyl)-lH- imidazo [4,5-c] [1,5]

naphthyridin-4-amine for imiquimod as an IRM and use it in cervical cap or suppository to treat cervical dysplasia. Each component is taught by the prior art to be useful for the same purpose, use of IRM for treating cervical dysplasia by applying it locally with either suppository or cervical cap. The idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).*

One would be motivated to make this combination of the said references to benefit from transmucosal delivery of the IRM to modulate TRL7 pathway to treat cervical dysplasia. Given the state of the art as evidenced by the teachings of the cited references and there would have been a reasonable expectation of success in combining the teachings of the cited references to obtain a localized nonirritant application of IRM compound to treat cervical dysplasia.

Response to Applicants' arguments:

Applicants argued that '674 reference does not disclose or suggest using the devices in such a way as to fall within the present claims since claim 1 requires removing from the mucosal surface a substantial amount of the IRM ....". Applicants further stated this would not normally happen using a suppository, direct cervical applicator, or cervical cap because a drug formulation is normally released from such devices before they are removed and unless intentionally designed to remove the drug formulation along with the device, e.g., by having the IRM drug adhered to the device so it does not get easily separated, the IRM drug formulation will normally be released from the device and not removed from the mucosal surface when the device is removed.

However, applicants' arguments are not deemed to be persuasive. In view of the instant specification, the suitable devices used for the IRM drug in the instant invention include cervical caps, diaphragms, and solid matrices such as tampons, cotton sponges, cotton swabs, foam sponges, and suppositories, which are well-known removable cervical devices, and the IRM drug is simply applied or impregnated to those devices (p16, line 19-p17, line 2). Thus, the instant invention as claimed does not have non-obvious features as stated above in the argument since it uses usual cervical delivery devices, which are known to be removable after insertion and the IRM drug formulation is applied or impregnated to those device as known in prior art. The following references are cited for evidentiary purpose to show the state of the art.

US 6328991 teaches a removable vaginal device such as vaginal sponge impregnated with a solution containing a carrier and an active pharmaceutical agent for vaginal infections, which releases active agents throughout the vaginal canal while being inserted and is removed (abstract, column 4, lines 40-57, and column 6, lines 1-64). US 4393871 also teaches a vaginal device adapted for insertion and placement in the human vaginal cavity and subsequent removal therefrom for the administration of a variety of medications such as anti-infectives, anti-inflammatories, estrogens, progestogens, and the like (abstract).

Therefore, the use of removable cervical devices for delivering an IRM drug to a mucosal surface within vagina would have been obvious to one of ordinary skill in the art at the time the invention was made and one skilled in the art would have known that the device could be removed after insertion within a certain time period and the substantial amount of the drug applied to the device, which is not absorbed by mucosal surface, would be removed along with the device as stated in the previous action.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00-6:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614
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